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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

SUBJECT: PP#9G2154/9H5201. Pirimiphos-methyl on stored peanuts. Amendment of 3/10/83.

TO: Jay Ellenberger, Product Manager #12
Insecticide-Rodenticide Branch
Registration Division (TS-767)

and

Toxicology Branch,
Hazard Evaluation Division (TS-769)

Linda S. Propst for

FROM: Nancy Dodd, Chemist
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THRU: Charles L. Trichilo, Chief
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I.C.I. Americas, Inc. resubmits Sections D and F for PP#9G2154/9H5201 on stored peanuts.

Deficiencies which RCB found in PP#9G2154/FAP9H5201 for peanuts were listed in the review of 2/14/80 and in the EPA letter to the company which was dated 3/25/80. The deficiencies were clarified in the conference of 6/20/80 (RCB memo of 7/2/80). Deficiencies as of 7/2/80, the petitioner's response, and RCB's conclusions are below.

Deficiency #1:

The proposed 10 parts per million (ppm) tolerance level for residues in peanuts is not adequate to cover the highest expected residue levels of pirimiphos methyl and its metabolites. A 25 ppm tolerance level would be appropriate.

Petitioner's response to deficiency #1:

The petitioner submits a revised Section F with a temporary tolerance proposal of 25 ppm on peanuts.

Conclusion #1:

Deficiency #1 is resolved.

Deficiency #2:
The tolerance regulation should be revised to include the following compounds:

pirimiphos-methyl (I),
0-2-ethylamino-6-methyl-pyrimidin-4-yl 0,0-dimethyl phosphorothioate (II),
2-diethylamino-6-methyl-pyrimidin-4-ol (IV),
2-ethylamino-6-methyl-pyrimidin-4-ol (V),
and 2-amino-6-methyl-pyrimidin-4-ol (VI).

Petitioner's response to deficiency #2:

The petitioner submits a revised Section F to include "combined residues of the insecticide pirimiphos-methyl, 0-(2-diethylamino-6-methyl-pyrimidin-4-yl)0,0-dimethylphosphorothioate, the metabolite 0-(2-ethylamino-6-methyl-pyrimidin-4-yl)0,0-dimethylphosphorothioate and, in free and conjugated form, the metabolites 2-diethylamino-6-methyl-pyrimidin-4-ol, 2-ethylamino-6-methyl-pyrimidin-4-ol, and 2-amino-6-methyl-pyrimidin-4-ol."

The petitioner requests that EPA reconsider the need to include conjugates of 0-(2-ethylamino-6-methyl-pyrimidin-4-yl) 0,0-dimethylphosphorothioate in the tolerance expression for the following reasons:

1. Metabolism studies do not provide evidence of formation of conjugates of this compound.

2. If conjugates of this compound were formed, they would be determined after conjugate cleavage as conjugated hydroxypyrimidines.

Conclusion #2: We concur with the petitioner's reasoning concerning conjugates of metabolite II.

Deficiency #2 is resolved.

Deficiency #3:

We are unable to determine whether adequate analytical methods are available to enforce tolerances for residues of the metabolites hydroxy pyrimidine (2-diethylamino-6-methylpyrimidin-4-ol) and des ethyl hydroxypyrimidine (2-ethylamino-6-methylpyrimidin-4-ol) in peanuts, peanut hulls, peanut oil and meat, milk, poultry and eggs. Validation data reflecting recoveries of these 2 metabolites from these commodities including sample chromatograms are needed.

Deficiency #4:

Suitable analytical methods are needed for the metabolite 2-amino-6-methylpyrimidin-4-ol in both free and conjugated form. Also, submit either suitable analytical methods for the conjugates of the metabolites 0,0-dimethyl-0-(2-ethylamino-6-methylpyrimidin-4-yl)phosphorothioate, 2-diethylamino-6-methylpyrimidin-4-ol and 2-ethylamino-6-methylpyrimidin-4-ol or data showing that the available methods for these metabolites determine conjugates. (The hydrolysis step which releases conjugates can be deleted in milk and eggs. Since 50% of the radioactive residue is free hydroxypyrimidines, the worst case would be 50% conjugated in milk and eggs.)

Petitioner's response to deficiencies #3 and #4:

The petitioner submits an analytical method for the hydroxypyrimidine metabolites (2-diethylamino-6-methyl-pyrimidin-4-ol,2-ethylamino-6-methyl-pyrimidin-4-ol, and 2-amino-6-methyl-pyrimidin-4-ol) in peanuts and animal products. The hydrolysis step for conjugates in milk and eggs is deleted as agreed by RCB. The analytical method (#47) is discussed below.

Analytical Method #47 (Reference ID and Appendix I):

Peanut Kernels - Peanut kernel samples are extracted with 50% methanol: 2M HCl. Centrifuge. The extract is shaken with hexane to separate phosphorothioate containing pyrimidines. The methanol is evaporated. Transfer the aqueous extract to a boiling tube and adjust the volume to form a 5M HCl solution with glass distilled water. The aqueous extract is refluxed while being heated for one hour to hydrolyze hydroxypyrimidine conjugates. The extracts are then neutralized with anhydrous sodium carbonate and buffered with a phosphate buffer. Then the extract is partitioned with butanol using an Extrelut column. After cleanup by adsorption chromatography and reaction with N,0-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) in pyridine to form trimethylsilyl derivatives, residues are analyzed by gas chromatography-mass spectrometry.

Recoveries of Compounds IV, V, and VI were determined in peanut kernels at fortification levels of 0.05-1.0 ppm. Recoveries were 82-98% for compound IV, 77-95% for Compound V, and 75-93% for Compound VI.

The limit of detection of the method is 0.01 ppm.

Tissues - Tissues samples are extracted with 50% methanol:2M HCl. Centrifuge. The extract is shaken with hexane to separate phosphorothioate containing pyrimidines. The methanol is evaporated. The aqueous extract is refluxed while being heated for one hour to hydrolyze hydroxypyrimidine conjugates. The extracts are then neutralized with anhydrous sodium carbonate and buffered with a phosphate buffer. Then the extract is partitioned with butanol using an Extrelut column. After cleanup by adsorption chromatography and reaction with N,0-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) in pyridine to form trimethylsilyl derivatives, residues are analyzed by gas chromatography-mass spectrometry.

Recoveries of 2-diethylamino-6-methyl-pyrimidin-4-ol (compound IV), 2-ethylamino-6-methyl-pyrimidin-4-ol (Compound V, and 2-amino-6-methyl-pyrimidin-4-ol (Compound VI) were determined in animal tissues at fortification levels of 0.10-5.0 ppm. Recoveries in animal tissues (chicken muscle, cow muscle, liver, and kidney) at a fortification level of 0.1 ppm were 64-82% for Compound IV, 78-97% for Compound V, and 48-93% for Compound VI. Recoveries in animal tissues at a fortification level of 0.5 ppm were 70% for Compound IV, 72% for Compound V, and 53-72% for Compound VI.

The limit of detection of the method in tissues is 0.01 ppm.

Milk - Extract milk (20 g) with a mixture of concentrated HCl (5 ml), methanol (25 ml), and hexane (20 ml). Centrifuge. Evaporate the aqueous phase to remove methanol. Then neutralize with 5M sodium hydroxide and solid sodium carbonate. Buffer the aqueous phase with phosphate buffer and partition with butanol using an Extrelut column. After cleanup by adsorption chromatography and reaction with N,0-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) in pyridine to form trimethylsilyl derivatives, residues are analyzed by gas chromatography-mass spectrometry. There is no hydrolysis step for milk.

Recoveries of Compounds IV, V, and VI were determined in cow milk at fortification levels of 0.0025-1.0 ppm. Recoveries in milk at a fortification level of 0.1 ppm were 114% for Compound IV, 101% for compound V, and 99% for Compound VI.

The limit of detection of the method in milk is 0.01 ppm.

Eggs - Extract eggs in a mixture of 90% methanol:10% 2M HCl. Centrifuge. Shake the supernatant with hexane. Evaporate the bottom layer to dryness. Redissolve the residue in a pH 7 phosphate buffer. Partition with butanol using an Extrelut column. After cleanup by adsorption chromatography and reaction with N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) in pyridine to form trimethylsilyl derivatives, residues are analyzed by gas chromatography-mass spectrometry. There is no hydrolysis step for eggs.

Recoveries of Compounds IV, V, and VI were determined in eggs at a fortification level of 0.05 ppm. Recoveries were 76-118% for Compound IV, 67-112% for Compound V, and 65-106% for Compound VI.

The limit of detection of the method in eggs is 0.01 ppm.

Conclusions #3 and #4:

a. Previously submitted methods were found adequate for enforcement of the temporary tolerances of parent and O-(2-ethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethylphosphorothionate on peanuts, meat, milk, poultry, and eggs (see memo of Dr. R. Perfetti and Dr. R. Hummel, 3/29/79).

b. The submitted analytical method #47 is adequate to determine free and conjugated hydroxypyrimidines (Compounds IV, V, and VI) in peanut meat, meat, milk, poultry, and eggs.

c. As indicated in Conclusion #2, conjugates of metabolite II are not expected to comprise a significant portion of the terminal residue. Therefore, separate methodology for conjugates of metabolites II is not needed.

Deficiency #5:

Any final conclusion regarding the adequacy of the proposed tolerance for meat remains contingent upon the availability of appropriate methodology and validation data for the parent compound and its significant metabolites.

Petitioner's response to deficiency #5:

Temporary tolerances of 0.1 ppm for meat, milk, poultry, and eggs except liver and kidney and 0.3 ppm for liver and kidney are proposed.

Conclusion #5: These tolerance levels were agreed upon at the conference of 7/2/80 and are still considered appropriate. Deficiency #5 is resolved.

Recommendations

Toxicological considerations permitting, we recommend that temporary tolerances/food additive tolerances be established for combined residues of the insecticide pirimiphos-methyl, 0-(2-diethylamino-6-methyl-pyrimidin-4-yl) O, O - dimethyl-phosphorothioate, the metabolite 0-(2-ethylamino-6-methyl-pyrimidin-4-yl) 0,0-dimethylphosphorothioate and, in free and conjugated form, the metabolites

2-diethylamino-6-methyl-pyrimidin-4-ol
2-ethylamino-6-methyl-pyrimidin-4-ol and
2-amino-6-methyl-pyrimidin-4-ol
in or on the following agricultural commodities:

Peanuts	25	ppm
Peanut hulls	125	ppm
Milk, eggs, and the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep (except liver and kidney)	0.1	ppm
Liver and kidney of cattle, goats, hogs, horses, poultry and sheep	0.5	ppm
Peanut oil (food additive tolerance)	50	ppm

Since a petition (PP#3F2896) requesting permanent tolerances for residues of pirimiphos-methyl in or on peanuts is currently awaiting review, we will not list any permanent tolerance requirements.

cc: R.F.
Circu
Reviewer
TOX
EEB
EAB
Petition No. 9G2154/9H5201
FDA
Robert Thompson

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